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COMPARATIVE STUDY OF CHOLERETIC AGENTS IN ANESTHETIZED
RATS AS WELL AS IN RESTRAINED AND UNRESTRAINED RATS,
WITH OR WITHOUT COMPENSATION FOR BILIARY LOSS

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16. Abstract Tests were conducted on Wistar rats by using 3 control choleretic agents: 1-phenyl-1-hydroxy n-pentane, dehydrocholic acid, and phenyl-dimethylacetic acid. The effects of these agents were compared in different experimental conditions. The comparative study of choleretic agents in anesthetized rats, in restrained and unrestrained rats, with or without compensation for biliary loss by the biliary secretion of restrained or unrestrained rats does not show, in systematic pharmacodynamic investigations, an obvious superiority over the methods based on the simple technique.		
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Variations in bile volume, flow of bile salts and of bilirubin subsequent to the rat's tranquilization, restraint, or setting free, with or without compensation for biliary loss, have recently been determined [1]. Certainly, objections addressed to studies on choleresis made when the animals are asleep are well known. However, it does not appear that using unanesthetized but restrained rats improves anything: biliary flow remains low, elimination of bilirubin increases, loss of biliary salts is evident. But a technique using unrestrained animals, in which a catheter placed in the duodenum permits the gathering of bile from the donor subject, appeared quite satisfactory. /842*

The question of whether, in the domain of pharmacology, the systematic realization of this process with all its complexity is efficient enough to be used systematically in preference to a priori methods that are more vulnerable to criticism but also simpler, is constantly at issue. The object of this project is thus to respond to such an inquiry. To do this, three reference choleretic agents were employed: 1-phenyl-1-hydroxy n-pentane, dehydrocholic acid, and lastly, phenyl dimethylacetic acid. Their effects were compared under various experimental conditions.

Method of Study

We used male Wistar rats of the same stock with a mean weight of 300 ± 20 grams, grouped in lots of twelve to sixteen subjects. The experiment was always preceded by a water fast of 18 hours in individual cages. The products were administered by esophageal

* Numbers in the margin indicate pagination in foreign text.

intubation in doses of 100 mg/kg, after 90 minutes of observation permitting the gathering of three bile samples, one every thirty minutes.

Five different situations were created for the subjects on whom some technical data had already been taken. Different groups of rats were: 1) anesthetized with ethyl carbamate, 2) prepared with ether, then kept under restraint, 3) left unrestrained after the above preparation, 4) left unrestrained but receiving the biliary secretion of animals kept under restraint, 5) lastly, left unrestrained with the donor subjects unrestrained as well. We must emphasize that, in the final lots, the donor animals were treated with the same doses within the same amount of time as the recipient rats.

Results and Discussion

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a. Variation of Bile Flow

Percentages of maximum augmentation of the bile flow in relation to the average basal secretion of the group is shown in the table:

Products	Experimental protocol				
	Anesthe- sia	Restrained	Unres- trained w/o donor	Unres- trained w/rest. donor	Unres- trained w/free donor
Phenylhydroxy n-pentane	33%	52%	63%	32%	54%
dehydrocholic acid	16%	18%	23%	13%	9%
Phenyldimethyl- acetic acid	71%	79%	56%	111%	119%

If it is impossible to distinguish the effects of the first two cholagogues after experimental conditions have been imposed, it is not the same for phenyl-dimethylacetic acid. Not only is the intensity of the action augmented for donor rats, as the figures show, but also its duration is greatly prolonged. The increase of flow, in effect, practically disappeared after the third hour in the first three groups, while they remained at 76 and 67% in the two last groups.

b. Variations in Elimination of Biliary Salts

Two facts stand out in this study: for one, no significant difference exists between the results obtained for one product using various methods; for the other, none of the three substances is a true cholagogue -- that is, capable of increasing the rate of excretion of bile salts.

c. Variations in Elimination of Bilirubin

Here, too, we found nothing of interest from the new methods proposed in relation to the cells of the drugged animals by examining the three cholagogues selected. Invariably, the rate of elimination of bilirubin in restrained rats increased progressively to attain ultimately five or six times the initial value by the fourth hour of the test. However, two hours after restraining them and thirty minutes after their oral administration, the phenylhydroxy-n-pentane and the phenyl-dimethylacetic acid provoked a reduction of the hypersecretion of bilirubin. This phenomenon did not exist in the case of the dehydrocholic acid, of which the lack of efficacy on the biliary flow after oral administration also appeared in the table. No satisfactory explanation can be found for the power of the first two cholagogues in this area.

In conclusion, we return to the hypothesis of this work. It appears, in view of these results, that there are no certain

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advantages in employing the most complex method proposed for a first study of a choleric substance or a substance reputed to be so. One must take note in particular that esophageal administration in the anesthetized rats brings about results which differ little from those in an awakened subject, if one considers only the percentages of increase.

But when one wants to know a choleric agent better, it seems desirable to get as close as possible to normal physiological conditions, be it only for the stability of biliary excretion. Moreover, an increase of the effects in amplitude and duration in the case of unrestrained donor rats coupled with unrestrained recipients will permit the choice between two hypotheses. It is a question either of a true choleric agent and the accumulated excretion of biliary salts in the donor elevating the biliary secretion of recipient rats, or there being born an animal of active metabolism with a hepato-biliary elimination tract.

To sum up, the study of the effects of three choleric agents on anesthetized rats which are restrained or unrestrained, with or without compensation for biliary leakage with the biliary secretion of a restrained or unrestrained donor does not show any manifest superiority of elaborate methods over the most simple technique for application to systematic pharmacodynamic research. It always seems desirable to approach normal physiological conditions as closely as possible, in order to better study the effects of a recognized choleric. The technique using free rats in which biliary loss is compensated for by free donors fills this need well.

References

1. Labrid, D., Dureng, G., Tachon, J., Lambert, J., and Duchene-Marullaz, P., C.R. Soc. Biol. 164, 1708 (1970).